

Methadone maintenance treatment and mood disturbances: Pharmacological and psychological implications

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Summary

The rationale for methadone maintenance is to stabilise the pharmacological condition of illicit opioid users, thereby providing an opportunity to normalise health and social functioning. The extent to which methadone is effective for any given individual may be governed by the degree to which methadone prevents opioid withdrawal symptoms, in the absence of significant opioid adverse effects. Mood and anxiety disorders are common within opioid-dependent patients, and there is some evidence to suggest that these disorders may affect the response to treatment. This paper will describe the relationship between plasma (S)- and (R)- methadone concentration, opioid withdrawal, and state and trait mood disturbance. A series of studies have demonstrated that significant mood changes occur in response to changes in plasma methadone concentration, and that these mood changes are more pronounced in those who experience opioid withdrawal. Concentration-effect relationships suggest that relatively small changes in plasma concentration result in significant mood change. An important implication from this research is that consideration of individual differences in methadone pharmacokinetics is necessary for understanding the aetiology of observed mood disturbance among methadone dependent patients. Implications for the clinical management of methadone patients, including the assessment of, and response to, mood disorders and the implications for therapeutic drug monitoring within methadone maintenance programs will be discussed.

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At the time of commencing methadone maintenance treatment most heroin users display significant tolerance to the positive effects of heroin (e.g. euphoria), and much of the use of heroin is to avoid uncomfortable withdrawal symptoms (including feelings of dysphoria and anxiety). For many, the decision to enter treatment is also made in the context of significant social, legal, medical and psychological problems that

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have developed as a consequence of illicit drug use. It is perhaps of little surprise that clinically significant levels of mood disorders have been observed among opioid users in treatment and non-treatment settings. Methadone can improve the mood of these patients in part by relieving opioid withdrawal, but also by facilitating an improvement in social, legal and health status. However, for many methadone patients mood disturbances persist during treatment. The extent to which methadone is effective for any given individual may be governed by the degree to which the daily methadone dose prevents opioid withdrawal symptoms in the absence of significant opioid adverse effects, and this in turn may affect mood state. This paper presents a series of studies with methadone maintenance patients in which acute mood disturbances were compared with changes in plasma methadone concentrations during the inter-dosing interval. The implications arising from these studies for the diagnosis of clinical depression among methadone maintenance patients will be also presented.

In an initial study⁽⁴⁾, approximately one-third of a representative sample of patients in a public methadone maintenance program who had been stabilised on oral methadone doses averaging 60 mg/day regularly experienced withdrawal symptoms toward the end of each inter-dosing interval (designated 'non holders'). These patients could not be differentiated from those who were responding well to methadone (designated 'holders') by demographic, health, other drug use or treatment related variables. In a subsequent study⁽³⁾, subjective (opioid withdrawal severity, MBG scale of the Addiction Research Center Inventory, pain threshold in response to electrical stimulation to the ear) and objective (pupil diameter, respiration rate) opioid responses were measured at multiple time periods over a single inter-dosing interval and blood samples were collected for the determination of plasma methadone concentration. There were very few pharmacokinetic differences between the holders and non holder patient groups. There were neither significant differences in peak or trough plasma methadone concentrations, nor the relative proportions of patients with trough plasma methadone concentrations below 400 ng/mL. The patients did not differ on oral methadone dose level, demographic or other individual characteristics. The areas under the plasma methadone concentration - time curve were similar between the groups suggesting that total racemic methadone clearance and bioavailability were similar. However, there was evidence to suggest that the volume of distribution (VOSS) was smaller in non holders, suggesting a shortened terminal half-life ($t_{1/2}$) and corresponding shortened period of direct opioid effect among these patients.

Analyses of plasma concentration-effect relationships for the subjective responses demonstrated that small changes in the plasma methadone concentration translated into relatively large changes in these measures. The differences in withdrawal severity between the holder and non holder patient groups was related to the significantly more rapid rate of decline in plasma concentration during the period from the peak plasma concentration (approximately three hours after dosing) to trough (approximately 24 hours after dosing) among the non holders. We have recently demonstrated that alpha1-acid glycoprotein (AAG) levels were elevated in a sample of non-holders, suggesting

that the plasma protein binding of methadone was greater among these patients. As the free fraction of methadone determines the extent of direct opioid effects, such a finding might explain the more rapid rate of plasma methadone concentration decline in non holders. However, as AAG is a reactant protein, further research is required. Finally, a re-analysis of these data demonstrated that a greater relative exposure to (S)- versus (R)-methadone was associated with a greater intensity of opioid withdrawal, among patients maintained on at least 60 mg rac-methadone ⁽⁶⁾.

For many methadone patients, the daily methadone dose is associated with immediate and positive changes in mood state, while signs of anxiety are associated with trough methadone concentrations. In a recent study ⁽²⁾ the mood states of methadone maintenance patients were assessed over a complete inter-dosing interval, and compared with a group of non-opioid using controls. Mood states were assessed using the Profile of Mood States (POMS) ⁽⁵⁾ which is a list of 65 adjectives corresponding to six empirically derived subscales, five reflecting negative mood states (depression, tension, anger, fatigue, confusion) and one reflecting positive mood state (vigour). Summing these scores, weighting vigour negatively, provides a global estimate of total mood disturbance. It was found that there were significant changes in mood states during the inter-dosing interval, and these were associated with the plasma methadone concentration-time profile. In comparison with the relatively stable intensity of mood states reported by the controls, methadone patients experienced significant fluctuations in the intensity of mood states throughout the 24-hour period. For methadone patients, the period in which positive mood state (vigour) was closest to those of the controls corresponded with peak methadone plasma concentrations, and then declined throughout the remainder of the day, returning to baseline levels approximately 6 hours after the dose. Negative mood states (such as depression, anger and confusion) showed an inverse pattern, being lowest at the time of the peak plasma methadone concentration and peaking towards the end of the inter-dosing interval. However, even at peak methadone plasma concentrations, methadone patients reported significantly less of the positive mood states and significantly more of the negative mood states than drug-free controls, indicating that patients' mood state never attained control values. Once again, analyses of plasma methadone concentration-effect relationships demonstrated that small changes in plasma methadone concentrations translated into relatively large changes in mood states. Non holders displayed significantly greater mood disturbance than holders, and this was related to a significantly greater rate of decline in plasma concentration from peak to trough ⁽²⁾.

Patients reporting significant opioid withdrawal and mood disturbance, despite seemingly adequate oral methadone dose levels and trough plasma methadone concentration, are at risk of a poor treatment outcome. The standard clinical practice when responding to these patients is to increase the level of the daily methadone dose. However, these studies suggest that for a significant proportion of patients, such an approach is likely to be ineffective. This argument is based upon the finding that patients reporting opioid withdrawal toward the end of the inter-dosing interval often have higher peak plasma

methadone concentrations, and thus more intense subjective direct effect. This is in turn related to a shortened terminal half-life, producing a shortened period of feeling 'normal' and withdrawal in the latter part of the 24-hour inter-dosing interval^(3; 2; 7). It is hypothesised that a methadone dose increase might not change this situation, and might expose the patients to increased direct opioid effects. Rather the answer might be to either shorten the dosage interval or prescribe a longer acting opioid such as slow-release oral morphine. In a recent study, 10 methadone patients were identified as non holders by assessing subjective and objective opioid responses at multiple time periods over a single inter-dosing interval with concomitant analysis of plasma methadone concentration. These patients then received a divided daily methadone dose (50% of current dosage administered at 10:00 h and 15:30 h) for a period of two weeks and were then re-assessed to examine the relationship between the modified plasma methadone concentration-time profiles and mood disturbance. It was found that such a dosage regimen effectively flattened the plasma methadone-concentration-time profile without changing the trough plasma methadone concentration. Importantly it was found that the severity of opioid withdrawal and the intensity of mood disturbance were significantly reduced by the divided dose regimen, leading to significant improvements in health and social functioning. However, these clinical improvements were lost as patients were returned to the standard once-daily dosage regimen. These data demonstrate significant outcome benefits from reducing fluctuations in the plasma methadone concentration - time profile.

Such acute changes in mood state during the inter-dosing interval may also have important implications for the diagnosis of primary mood disorders, such as depression, within this population. The effective treatment of people with both mental health problems and drug dependence is contingent upon accurate diagnosis, but it is necessary to differentiate primary psychological disorders from the psychological disturbances associated with the pharmacological sequelae of opioids, as these two aetiologies require very different therapeutic strategies. However, the majority of current systems and instruments used in the assessment of people with both mental health and drug use problems have been developed within population representing only one of these conditions, making the validity of diagnoses uncertain. The Beck Depression Inventory-II (BDI-II)⁽¹⁾ is a valid and reliable 21-item self-report instrument that assesses the symptoms of depressive disorders as defined by the DSM-IV. In a current study, 520 methadone patients completed the BDI-II and the Subjective Opioid Withdrawal Scale. Confirmatory factor analyses on BDI-II data indicated that a 3 dimensional model with cognitive, affective and somatic symptoms loading on separate factors provided the best fit. It was found that the mean total BDI-II score for these patients (21.8 ± 12.7) was at the lower end of the "severe" range and similar to that obtained for males entering residential drug detoxification treatment ($22.1, p=.619$), but significantly higher than: college students ($12.6; p<.001$), and psychiatric patients with anxiety disorders ($19.4; p<.001$) or adjustment disorders ($17.3; p<.001$)⁽¹⁾. However, regression analyses demonstrated that opioid withdrawal ($b=1.46, P<0.01$), the number of days of health

problems ($b=.29$, $p<0.001$), and the total number of illicit drugs used in the previous month ($b=1.59$, $p<0.05$) were significant predictors of scores on the BDI-II for these methadone patients. The model had significant predictive power ($F(4,77)=11.6$, $p<0.001$) and accounted for 37.6% of the variability in depression scores. Furthermore, for the non-holders receiving a divided daily methadone dose there was a 48% reduction in BDI-II total scores, which then reverted to original levels when the patients resumed the once-daily dosage regimen. In conclusion, these studies suggest that the use of the BDI-II by itself cannot distinguish between depression and opioid withdrawal, highlighting the difficulty in measuring diagnostically relevant psychiatric conditions among methadone patients.

Methadone patients display considerable mood disturbance, with the severity of this disturbance being associated with fluctuations in plasma methadone concentration, rather than a function of time in treatment or other factors. An important implication from these studies is that consideration of individual differences in methadone pharmacokinetics is necessary for understanding the aetiology of observed mood disturbance among methadone dependent patients. Methadone patients will display significant depression, anxiety, anger, confusion and fatigue toward the end of each dosage interval and for non-holders such mood disturbance will persist during the day. These patients might best be considered as in an almost chronic state of opioid withdrawal that is diminished partly by the administration of the daily methadone dose. In terms of the diagnosis of psychological disorders, these data demonstrate that reliance upon single interviews and self-report forms may be affected by transient symptoms, and will thus overestimate the prevalence of these disorders among this population. Nevertheless, chronic pronounced negative mood coupled with significant daily fluctuations in mood state, may make normal social functioning extremely difficult. As such, to identify primary mood disorders we need to be mindful of opioid withdrawal severity and the patients' response to methadone. Accurate diagnosis of clinical depression among methadone patients requires individualised behavioural, psychometric and psychosocial assessment (including assessment of opioid withdrawal symptomatology). Although intensive, such an assessment will provide the necessary information to develop an effective individualised treatment program.

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